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Role of Topical Corticosteroid in Bacterial-Fungal Polymicrobial Corneal Ulcer: A Case Report

I Gusti Ngurah Agung Wisnu Kresnan Dana, Priscilla Christina Natan, and Luh Putu Eka Naryati

ABSTRACT

Corneal ulcers are the loss of the corneal layer which can be caused by bacteria, fungi, viruses or parasites. In this case, a 53-year-old man with corneal ulcer in the left eye after using antibiotic and steroid eye drops. Physical examination showed blepharospasm, conjunctival and ciliary injection. There was an ulcer on cornea with the size 5 mm × 6 mm, indistinct boundaries with infiltrates, corneal edema, and 2 mm of hypopyon. The results of gram and KOH examination on corneal scraping showed the presence of hyphae, spores, and gram-positive coccus bacteria. Initial treatment with natamycin eye drop, levofloxacin and atropine eye drop for 3 months showed clinical improvement. Administration of steroid eye drop in this case aims to reduce inflammation after adequate treatment with antibiotics.

Keywords: Bacterial keratitis, fungal keratitis, topical steroids, ulcerative keratitis.

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I. Introduction

Keratitis is an inflammation of the cornea that can worsen if proper treatment is not given leading to blindness. Keratitis can be caused by both infectious and noninfectious processes; therefore, the diagnosis and management cases are challenging. Microbial keratitis can be caused by bacteria, fungi, viruses or parasites that damage the lining of the cornea and then cause ulcers [1]. Corneal ulcer is the loss part of the corneal surface due to damage the corneal tissue [2]. This is one of the main causes of visual impairment and blindness worldwide [3]. The epidemiology of corneal ulcers as a cause of blindness in the world varies in each country. In developing countries estimated that 1,5 to 2 million cases. The incidence of microbial keratitis varies from 11 per 100.000 population per year in United States to 799 per 100.000 population per year in other developing countries [4].

Mixed infection of more than one bacteria or combination of bacteria and fungal or parasites (polymicrobial) is rare, ranging from 1,9% to 15,8% [5]. A study in India, bacterial were found in keratomycosis from 5% to 25%. Other laboratories in South America and Asia found bacteria in approximately 30% to 60% of corneal specimens with fungal keratitis [6]. Fungal keratitis was more common in tropical than subtropical areas with a predisposition to contact with plants, and fungi was a sensitive disease that sensitive to temperature and weather [7]. Microscopic examination and culture were performed to diagnostic polymicrobial keratitis.

II. Case Illustration

A 53-year-old male patient came to the eye clinic Mangusada Hospital on August 2022 with complaints of blurry, red, sore left eye and had gotten worse for 2 weeks, a history of using steroid combination antibiotic eye drops in the form of neomycin sulfate, polymyxin B, and dexamethasone which bought by himself. History of used eye drop 3 times daily but the patient can't remember how long it has been used. Patient was a construction worker who has risk of being exposed to dust every day and without wearing glasses while working, history of trauma was unclear. History of hypertension and diabetes was denied. Preliminary visual acuity examination of the right eye 6/7,5 and left eye 1/300. The result of eyeballs evaluation was ortho-tropia and the movement were normal in all directions. Examination of anterior segment of the right eye found within normal limits, and the left eye found blepharospasm, conjunctival and ciliary injection, ulcer in central part of cornea with size 5 mm x 6 mm, poorly demarcated, with infiltrate and edema. Hypopyon was found in the anterior chamber of the left eye approximately 2 mm. Cornea sensibility was in normal limit. The left eye was examined for scraping cornea for gram and

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KOH examination. Medical therapy for the left eye was given levofloxacin eye drop every one hours, sodium chloride & potassium chloride eye drop four times daily, cyclopentolate eye drop 1% three times daily. Oral medication was given such as diclofenac sodium 50 mg twice daily, and ciprofloxacin 500 mg twice daily. All the previous eye drops by the patient was discontinued.

After 3 days of treatment, the complaints of the left eye still felt blurry and red, visual acuity on left eye was 1/60 with hypopyon in anterior segment about 1 mm. Corneal scraping result was found hyphae, spores, and gram-positive coccus bacteria. Additional 5% natamycin eye drop therapy was given every hour to the left eye, and orally fluconazole 150 mg once a day.

Two weeks after the initial treatment, the redness and pain in the left eye began decrease, the visual acuity 3/60, a central corneal ulcer still found with no hypopyon. Fluorescein test was still positive, the pupil was mid-dilated due to the use of cyclopentolate 1% eye drop. Levofloxacin and natamycin eye drops reduced to six times daily in the left eye. Additional sodium hyaluronate eye drop starts with four times daily in the left eye.

Two months from the initial treatment, there were no complaints of pain but sometimes a lump was felt in the left eye, there was a sharp improvement in left eye vision to 6/45, anterior segment examination found corneal scar and minimally edema. Continued therapy was used levofloxacin four times daily, sodium chloride & potassium chloride four times daily, and prednisolone acetate four times daily.

Three months after treatment, visual acuity of left eye 6/45 and the complaints were limited to discomfort of the left eye with scar of cornea. Treatment continued with artificial tears that used four daily such as, sodium & potassium chloride eye drop and sodium hyaluronate eye drop. Based on clinical appearance and the results of the corneal scraping, this patient was concluded to have bacterial and fungal corneal ulcers.

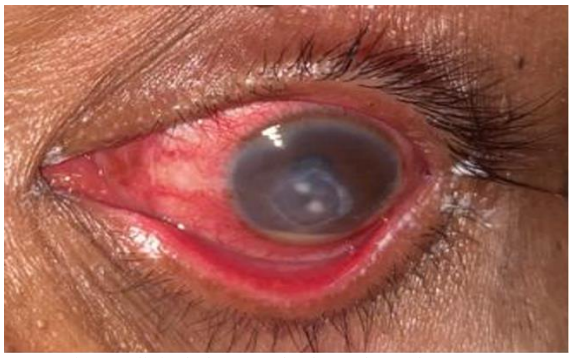

Fig. 1. Clinical photograph after 3 days of treatment.

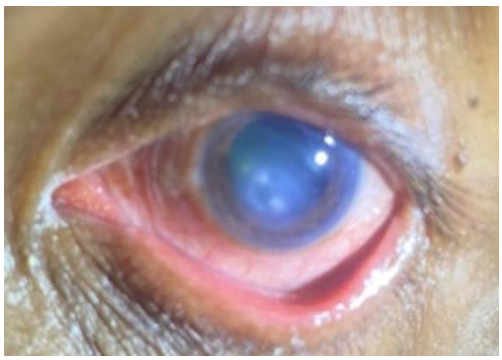

Fig. 2. Clinical photograph after 2 weeks treatment.

Fig. 3. Clinical photograph after 2 months treatment.

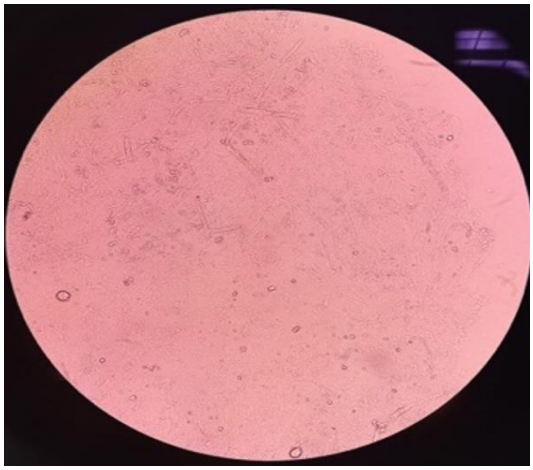

Fig. 4. KOH examination showed spores and hyphae.

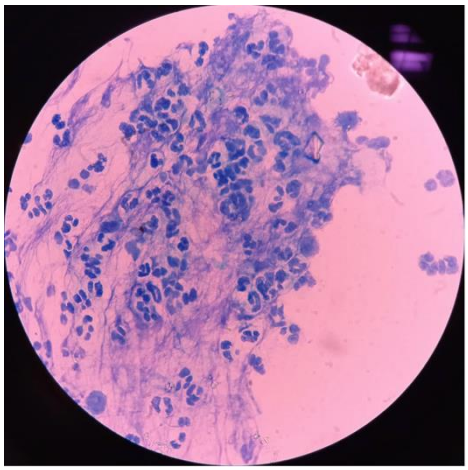

Fig. 5. Gram staining photograph showed gram-positive coccus bacteria.

III. Discussion

Based on the description of the case, an inflammatory condition of the cornea with the presence of hypopyon, and the results of the corneal scraping in this case were concluded to have a mixed corneal ulcer due to bacterial and fungal. Corneal scraping with gram staining and culture is the gold standard for diagnosis of bacterial keratitis [1]. This is in accordance with previous studies corneal ulcers (ulcerative keratitis) can caused by bacteria, fungi, viruses, or parasites [3]. Ulcers can occur due to damage to the corneal epithelial tissue layer with stromal infiltration which is characterized by inflammation with or without hypopyon [2], [8]. Based on the study of Muhammad Asroruddin et al, the most common

causes of bacterial corneal ulcers or bacterial ulcerative keratitis are *Streptococcus*, *Pseudomonas*, and *Staphylococcus*. The last 20 years at Cipto Mangunkusumo Hospital found *Pseudomonas aeruginosa* (49%), *Staphylococcus epidermidis* (24%), however in the last 10 years *Staphylococcus epidermidis* has dominated corneal ulcers [3]. The severity of ulcerative keratitis can be seen from the clinical condition and the pathogenicity of the infecting bacteria [4]. Because the culture study was not available in our hospital, the diagnosis can be established based on macroscopic and microscopic features. Clinical appearance of corneal ulcers that have hypopyon, satellite lesions, and unresponsive to antibiotics, are some signs that possibility of a mycotic agent. Direct microscopic examination of corneal scraping allows a rapid preliminary diagnosis. The diagnosis in this case was confirmed by the results of gram and KOH examination although culture was not performed in this case.

The profile of mixed keratitis case according to Amrutha Kumari et al. study, 100 corneal ulcers were subjected to microscopic examination, 48% showed bacterial or fungal. Amount of 67% from ulcers showed positive bacterial culture. A total of 45 (67,17%) found bacteria, 17 (25,37%) were found fungal, and 5 cases (7,46%) showed polymicrobial infection in which 4 cases showed the presence of fungi and bacteria. More than 20% of fungal keratitis is complicated by bacterial infection. In this study, 4 cases of bacterial and fungal infections with filamentous fungi were the most common cause of ulcerative keratitis. The causative agents of filamentous fungi vary depending on geographical location and weather. *Aspergillus spp* is the most common cause of fungal keratitis in India, Southern Iran, Nepal, and Bangladesh. *Fusarium spp* is the most common cause of fungal keratitis in South India with more severe clinical symptoms and unresponsiveness to therapy compared to *Apergillus* [9]. *S. epidermidis* and *Fusarium spp* is the most common combination of pathogens causing mixed keratitis [10]. The pathogenesis of mixed bacterial and fungal keratitis infection depends on the source and sequence of microbial exposure. The scientific article of J. C. Pate *et al.*, bacterial infection in fungal keratitis occurs three times more in the yeast phase compared to the filamentous phase. *Candida albicans* forms biofilms which provide opportunities for bacteria to attach and live. Bacterial contaminants in the eye either simultaneously or after fungal pathogens will exacerbate clinical complaints of fungal keratitis [6].

Filamentous fungal keratitis is more common in warm and humid areas. Risk factors for fungal keratitis include plant-based corneal trauma, contact lenses wear, prolong use of corticosteroids, chronic corneal erosion/ ulcers, chronic keratitis due to HSV virus infection, herpes zoster or atopic keratoconjunctivitis, immunosuppression, and corneal surgery [11], [12]. *Candida* species are the most common cause of yeast keratitis. Clinical appearance of early fungal keratitis is nonsuppurative infiltrate with grayish white, multifocal satellite infiltrate, with or without hypopyon. Fungal can affect the iris and the posterior chamber causing secondary angle closure glaucoma to pupillary block due to inflammation [11], [13].

Damage to the corneal epithelium due to trauma made it easier for bacteria to attach to the surface of the cornea, proliferate, and invade the stromal layer of the cornea. Inflammation, cytokines, chemokines, formation of inflammatory cells from limbal blood vessels and tears, metalloproteinase secretion which will result in keratolysis and corneal necrosis [4], [11]. Epidemiology of blindness due to corneal defects reaches 1,5 to 2 million new cases each year with majority of cases such as trauma and infectious keratitis [14]. Based on history taking this case showed patient's job was a construction worker with the risk of being exposed to dust every day. Previous studies found occupations that have a high risk of developing corneal ulcers are farmers or workers in agriculture. Study of Mamoni Baruah *et al.*, construction workers are the second risky occupation with 20% of 50 cases of corneal ulcers at Assam Medical College and Hospitals [8]. The patient's occupation in this case is a high risk because of the habit rarely using protective glasses while working.

The patient experienced improvement in visual acuity after being given antibiotic and antifungal eye drop for 2 months. In accordance with the most common etiology of bacterial corneal ulcers which can be caused by gram-positive and negative bacteria and administration of fluoroquinolone is an option for monotherapy. This class of antibiotics has good sensitivity for gram-positive and negative bacteria, good penetration and a longer half-life. Administration begins every 30-60 minutes as an initial dose, then tapering based on clinical response. Second-generation fluroquinolones (ciprofloxacin, ofloxacin) are sensitive to Pseudomonas, but less sensitive to gram-positive bacteria. Third and fourth-generation fluroquinolones (moxifloxacin, gatifloxacin, levofloxacin, besifloxacin) are used for gram-positive bacteria and atypical mycobacteria [3], [11]. Systemic antibiotics especially fluroquinolones are not used routinely in bacterial keratitis, only in suspected scleral and/ or intraocular involvement. Topical cycloplegia was given to provide comfort and prevent pupillary block due to inflammation [11]. In this study, patient was given levofloxacin eye drop therapy for 3 months with the initial dose being used every 1 hour then reducing the dose, giving systemic antibiotics group of fluoroquinolones to prevent intraocular infection. Administration of cycloplegia at the start of the treatment to prevent synechiae and pupillary block. After 3 months of the therapy, the patient showed clinical improvement.

Systemic antifungals were given as topical adjuvant therapy. Indications for administration if the ulcer is more than 5 mm with a stroma depth of more than 50%, bilateral infection, presence of scleritis with limbal involvement or endophthalmitis, infection in children, post keratoplasty infection, and impending perforation. Natamycin is a topical antifungal that has been approved by the US-FDA for treatment of eye fungal [14], [15]. The 5% natamycin eye drop preparation is the most commonly used for filamentous fungi [14]. The study of Sheng Qiu *et al.* reported that natamycin was more effective than variconazole or fluconazole in the treatment of fungal keratitis. Natamycin binds to ergosterol which an important component of fungal cell wall, and inhibits the growth of fungi [15]. According to WHO guidelines, natamycin eye drop 5% every hour is the most effective in the treatment of keratitis with hyphae findings on corneal scraping [8], [13]. Natamycin eye drop is

more favorable applying in early period fungal keratitis and sensitive for almost all types of fungal infection [15]. The patient was given natamycin 5% eye drop for 3 months showed improved vision and a good recovery rate [9]. This was in accordance with the case, given 5% natamycin therapy for 3 months.

Administration of corticosteroid eye drop in this case was started after 2 months from initial treatment. Steroid is used to reduce inflammation in patients. The process of ulceration begins with an acute phase of epithelial and stromal damage which will stimulate immune cells to produce cytokines, collagen, and growth factors. It will make keratocyte apoptosis and damage to collagen. After the acute infectious phase is over, the keratocytes are transformed into fibroblast to restore the integrity of the damaged tissue. However, the fibroblast is formed in unfavorable shape causing cornea become cloudy and formed ulcers. Steroid drop would inhibit neutrophil chemotaxis, collagenase, and cytokines resulting in ulceration and scarring. Therefore, the use of topical corticosteroids in keratitis is postponed because inhibition of neutrophils can worsen the condition of the infection, especially if treatment with antibiotics is inadequate [1]. Based on the theories, the patient in this case experienced a corneal ulcer due to prolonged use of steroids with complaints of red eyes without any initial examination from an ophthalmologist. Steroid administration should only be carried out after adequate antibiotic therapy has been provided and it only used to treat inflammation and edema of the cornea.

Adjuvant therapies such as corneal glue, patch grafts, and conjunctival flaps, amniotic membrane transplantation, and keratoplasty are used in chronic cases that are unresponsive or resistant to treatment [16]. The purpose of this procedure is to replace the damaged corneal surface with healthy corneal tissue. Transplantation of the amniotic membrane in scar tissue due to infectious keratitis will provide anti-inflammatory effects, accelerate reepithelization, and anti-angiogenic effects [17]. According to our study, there was no indication for amniotic membrane transplantation because of the good response to treatment.

IV. Conclusion

Ulcerative keratitis or corneal ulcers can be caused by bacteria, fungi, viruses, or parasites. The incidence of mixed keratitis due to bacteria and fungi was still challenge in diagnosis and therapy. Culture study is the gold standard for diagnosis, but due to limited facilities at the hospital, this study could not be done. Nevertheless, the diagnosis has been confirmed by gram and KOH examination. Failure of a single therapy regimen of antibiotics or antifungals in keratitis can be considered as mixed keratitis. In this study showed an improvement in visual acuity after adequate administration of antifungal eye drop and antibiotic eye drop, followed by administration of steroid eye drop after 2 months. The use of topical steroids is still being debated as an anti-inflammatory, before the use of steroids must be preceded by adequate topical antifungal and antibiotics.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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